

Claims

1 1. A method for making a water insoluble
2 biocompatible composition, said method comprising combining,
3 in an aqueous mixture, a polyanionic polysaccharide, a
4 nucleophile, and an activating agent under conditions
5 sufficient to form said composition.

6 2. The method of claim 1 wherein two or more
7 polyanionic polysaccharides are employed.

8 3. The method of claim 1 or 2 wherein said
9 polyanionic polysaccharides are chosen from the group
10 consisting of carboxymethyl cellulose, carboxymethyl
11 amylose, hyaluronic acid, chondroitin-6-sulfate, dermatin
12 sulfate, heparin, and heparin sulfate.

13 4. The method of claim 1 wherein said polyanionic
14 polysaccharide is hyaluronic acid.

15 5. The method of claim 1 wherein said polyanionic
16 polysaccharide is carboxymethyl cellulose.

17 6. The method of claim 1 wherein said polyanionic
18 polysaccharide is carboxymethyl amylose.

19 7. The method of claim 2 wherein two of said
20 polyanionic polysaccharides are hyaluronic acid and
21 carboxymethyl cellulose.

22 8. The method of claim 1 wherein said activating
23 agent is chosen from the group consisting of benzotriazole-
24 1-yloxytris(dimethylamino)phosphonium hexafluorophosphate,
25 O-benzotriazole-1-yl-N,N,N',N'-tetramethyluronium

26 hexafluorophosphate, bromotris(dimethylamino)phosphonium
27 hexafluorophosphate, bromotris(pyrrolidinyl)phosphonium
28 hexafluorophosphate and the corresponding halide salts
29 thereof.

30 9. The method of claim 1 wherein said polyanionic
31 polysaccharide are present in a concentration of 0.0002 -
32 0.1M.

33 10. The method of claim 9 wherein said polyanionic
34 polysaccharide is present in a concentration of 0.0005 -
35 0.02M.

36 11. The method of claim 1 wherein said method is
37 carried out at a pH 3.5 - 8.0.

38 12. The method of claim 1 wherein the stoichiometry
39 of said activating agent to said polysaccharide is at least
40 0.1 molar equivalent of said activating agent per molar
41 equivalent of said polyanionic polysaccharide.

42 13. The method of claim 1 wherein said nucleophile
43 is chosen from the group consisting of an amino acid amide,
44 a monofunctional amine, an amino acid ester, an amino
45 alcohol, an amino thiol, an amino phenol, an amino catechol,
46 an amino acid, a salt of an amino acid, a peptide, and a
47 protein.

48 14. The method of claim 1 wherein the stoichiometry
49 of said polyanionic polysaccharide to said nucleophile is at
50 least 1 molar equivalent of nucleophile per molar equivalent
51 of polyanionic polysaccharide.

52 15. A method for making a water insoluble
53 biocompatible composition, said method comprising combining,
54 in an aqueous mixture, one or more polyanionic
55 polysaccharides, a modifying compound, a nucleophile, and an
56 activating agent under conditions sufficient to form said
57 composition wherein said modifying compound causes the
58 formation of a new active carbonyl groups on said
59 polyanionic polysaccharide.

60 16. The method of claim 15 wherein two or more
61 polyanionic polysaccharides are employed.

62 17. The method of claim 15 or 16 wherein said
63 polyanionic polysaccharides are chosen from the group
64 consisting of carboxymethyl cellulose, carboxymethyl
65 amylose, hyaluronic acid, chondroitin-6-sulfate, dermatin
66 sulfate, heparin, and heparin sulfate.

67 18. The method of claim 15 wherein said polyanionic
68 polysaccharide is hyaluronic acid.

69 19. The method of claim 15 wherein said polyanionic
70 polysaccharide is carboxymethyl cellulose.

71 20. The method of claim 15 wherein said polyanionic
72 polysaccharide is carboxymethyl amylose.

73 21. The method of claim 16 wherein two of said
74 polyanionic polysaccharides are hyaluronic acid and carboxyl
75 methyl cellulose.

76 22. The method of claim 15 wherein said modifying
77 compound is chosen from the group consisting of

78 1-hydroxybenzotriazole hydrate, 1-hydroxybenzotriazole
79 monohydrate, N-hydroxysulfosuccinimide,
80 N-hydroxysuccinimide, 4-nitrophenol, 2-nitrophenol,
81 4-nitrothiophenol, 2-nitrothiophenol, pentachlorophenol,
82 pentafluorophenol, imidazole, tetrazole, and
83 4-dimethylaminopyridine.

84 23. The method of claim 15 wherein said activating
85 agent comprises a carbodiimide.

86 24. The method of claim 23 wherein said
87 carbodiimide comprises 1-ethyl-3-(3-dimethylaminopropyl)
88 carbodiimide, or 1-ethyl-3-(3-dimethylaminopropyl)
89 carbodiimide methiodide.

90 25. The method of claim 15 wherein said polyanionic
91 polysaccharide is present in a concentration of 0.0002 -
92 0.1M.

93 26. The method of claim 25 wherein said polyanionic
94 polysaccharide is present in a concentration of 0.0005 to
95 0.02M.

96 27. The method of claim 15 wherein said method is
97 carried out at a pH 3.5 - 8.0.

98 28. The method of claim 15 wherein the
99 stoichiometry of said polyanionic polysaccharide to said
100 activating agent is at least 0.1 molar equivalent of said
101 activating agent per molar equivalent of said polyanionic
102 polysaccharide.

103 29. The method of claim 15 wherein the
104 stoichiometry of said modifying agent to said activating
105 agent is at least 1 molar equivalent of said modifying
106 compound per molar equivalent of said activating agent.

107 30. The method of claim 15 wherein said nucleophile
108 is chosen from the group consisting of an amino acid amide,
109 a monofunctional amine, an amino acid ester, an amino
110 alcohol, an amino thiol, an amino phenol, an amino catechol,
111 an amino acid, a salt of an amino acid, a peptide, and a
112 protein.

113 31. A water insoluble composition prepared
114 according to the method of claim 1, 2, 15 or 16.

115 32. The composition of claim 31 wherein said
116 composition is in the form of a gel.

117 33. The composition of claim 31 wherein said
118 composition is in the form of fibers.

119 34. The composition of claim 31 wherein said
120 composition is in the form of a membrane.

121 35. The composition of claim 31 wherein said
122 composition is in the form of a foam.

123 36. The composition of claim 31 wherein said
124 composition is in the form of an adhesion prevention
125 composition.

126 37. The composition of claim 31, further comprising
127 a pharmaceutically active substance dispersed within said
128 composition.

129 38. The composition of claim 37 wherein said
130 pharmaceutically active substance is chosen from the group
131 consisting of proteins, growth factors, enzymes, drugs,
132 biopolymers, and biologically compatible synthetic polymers.

133 39. A water insoluble composition comprising the
134 reaction product of a polyanionic polysaccharide, a
135 nucleophile, and an activating agent.

136 40. A water insoluble composition comprising the
137 reaction product of two or more polyanionic polysaccharides,
138 a nucleophile, and an activating agent.

139 41. The water insoluble composition of claim 39 or
140 40 wherein said activating agent is chosen from the group
141 consisting of benzotriazole-1-yloxytris(dimethylamino)-
142 phosphonium hexafluorophosphate, O-benzotriazole-1-yl-
143 N,N,N',N'-tetramethyluronium hexafluorophosphate,
144 bromotris(dimethylamino)phosphonium hexafluorophosphate,
145 bromotris(pyrrolidinyl)phosphonium hexafluorophosphate and
146 the corresponding halide salts thereof.

147 42. A water insoluble composition comprising the
148 reaction product of a polyanionic polysaccharide, a
149 modifying compound, a nucleophile, and an activating agent.

150 43. A water insoluble composition comprising the
151 reaction or product of two or more polyanionic
152 polysaccharides, a modifying compound, a nucleophile, and an
153 activating agent.

154 44. The composition of claim 39, 40, 42 or 43
155 wherein said polyanionic polysaccharides are chosen from the
156 group consisting of carboxymethyl cellulose, carboxymethyl
157 amylose, hyaluronic acid, chondroitin-6-sulfate, dermatin
158 sulfate, heparin, and heparin sulfate.

159 45. The composition of claim 39 or 42 wherein said
160 polyanionic polysaccharide is hyaluronic acid.

161 46. The composition of claim 39 or 42 wherein said
162 polyanionic polysaccharide is carboxymethyl cellulose.

163 47. The composition of claim 39 or 42 wherein said
164 polyanionic polysaccharide is carboxymethyl amylose.

165 48. The composition of claim 40 or 43 wherein two
166 of said polyanionic polysaccharides are hyaluronic acid and
167 carboxy methyl cellulose.

168 49. The composition of claim 39, 40, 42 or 43
169 wherein said nucleophile is chosen from the group consisting
170 of an amino acid amide, a monofunctional amine, an amino
171 acid ester, an amino alcohol, an amino thiol, an amino
172 phenol, an amino catechol, an amino acid, a salt of an amino
173 acid, a peptide, and a protein.

174 50. The composition of claim 42 or 43 wherein said
175 modifying compound is chosen from the group consisting of
176 1-hydroxybenzotriazole hydrate, 1-hydroxybenzotriazole
177 monohydrate, N-hydroxysulfosuccinimide,
178 N-hydroxysuccinimide, 4-nitrophenol, 2-nitrophenol,

179 4-nitrothiophenol, 2-nitrothiophenol, pentachlorophenol,
180 pentafluorophenol, imidazole, tetrazole, and
181 4-dimethylaminopyridine.

182 51. The composition of claim 42 or 43 wherein said
183 activating agent comprises a carbodiimide.

184 52. The composition of claim 51 wherein said
185 carbodiimide comprises 1-ethyl-3-(3-dimethylaminopropyl)
186 carbodiimide, or 1-ethyl-3-(3-dimethylaminopropyl)
187 carbodiimide methiodide.

188 53. The composition of claims 39, 40, 42 or 43
189 wherein said composition is in the form of a gel.

190 54. The composition of claims 39, 40, 42 or 43
191 wherein said composition is in the form of fibers.

192 55. The composition of claims 39, 40, 42 or 43
193 wherein said composition is in the form of a membrane.

194 56. The composition of claims 39, 40, 42 or 43
195 wherein said composition is in the form of a foam.

196 57. The composition of claims 39, 40, 42 or 43
197 wherein said composition is in the form of an adhesion
198 prevention composition.

199 58. The composition of claims 39, 40, 42 or 43,
200 further comprising a pharmaceutically active substance
201 dispersed within said composition.

202 59. The composition of claim 58 wherein said
203 pharmaceutically active substance is chosen from the group
204 consisting of proteins, growth factors, enzymes, drugs,
205 biopolymers, and biologically compatible synthetic polymers.

202 59. The composition of claim 58 wherein said
203 pharmaceutically active substance is chosen from the group
204 consisting of proteins, growth factors, enzymes, drugs,
205 biopolymers, and biologically compatible synthetic polymers.